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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/469,492	06/06/95	WEINER H	1010/16959-U

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EXAMINER	
DUFFY,P	
ART UNIT	PAPER NUMBER
1645	27

DATE MAILED: 10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/469,492	Weiner et al
Examiner	**Group Art Unit**
DUFFY	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10-2-00 and 11-1-00.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 37, 38, 42-44, 46, 48, 52-54, 56+57 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 37, 38, 42-44, 46, 48, 52-54, 56+57 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

Response to Amendment

1. The amendment and declaration filed 10-2-00 and 11-1-00 have been entered into the record. Claims 37, 38, 42-44, 46, 48, 49, 52-54, 56 and 57 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

3. Any rejection not explicitly maintained herein is withdrawn based on Applicants' amendments.

Rejections Maintained

4. The rejection of claims 37, 38, 42-44, 46, 48, 49, 52-54, 56 and 57 under 35 U.S.C. 112, first paragraph is maintained for reasons made of record for claims 37-58 in Paper No. 6, mailed 12-31-96 and maintained in each office action thereafter.

Applicants have now broadened the claims to remove "not an autoantigen". The claims now recite "A method for treating an autoimmune disease in a human or rodent host by suppression an autoimmune response associated with said disease, the method comprising administering by nose or mouth to said host an effective amount for suppressing said response of a composition comprising a bystander antigen, wherein said bystander antigen is not an antigen to which T cells which mediated the disease are sensitized and wherein said bystander antigen is not an

insulin antigen." Other claims are further limited to "...wherein said bystander antigen is specific to an organ or tissue afflicted by immune attack during said disease.". These claims are still not enabled for the following reasons. Turning to the specification, treatment is specifically defined to encompass prevention of disease. The specification fails to teach that any level of suppression that could be achieved in any rodent or human is sufficient to prevent autoimmune disease. The art specifically teaches that in humans that even potent chemical immunosuppressant therapy is unable to prevent clinical onset of pre-Type I diabetes (Carel, et al. J. Autoimmun, 9:739-743, 1996). Therefore, applicants and evidence are not commensurate in scope with the specific definition of treatment as prevention of disease in the specification. The declaration of Dr. Von Herrath does not provide any evidence that any human disease can be prevented. Applicants arguments that the rejection based on treatment is not moot because, treatment is defined as prevention and substituting prevention by suppression of an autoimmune response is not enabled by this specification. Amendment of the claims to recite: "A method for suppressing an autoimmune response associated with an autoimmune disease in a human or rodent host having said autoimmune disease, the method comprising administering...". would obviate this issue. The next issue is directed to the representative working embodiments with in the claim. Applicants extensively argue that in their rodent model PLP is the autoantigen and MBP is the bystander. While this experimental model defines a functional relationship of autoantigen and bystander antigen for a rodent model

for multiple sclerosis, it does not suffice for the human. As previously set forth, both of these are autoantigens (Cohen ed, Autoimmune Disease Models, page 2) and *T-cell reactivity to both of the antigens have been demonstrated in multiple sclerosis patients* (Hafler et al., J Immunology, 139:68, 1987) and were recognized autoantigens at the time of applicants invention. Because humans with multiple sclerosis have activated T cells directed to PLP and MBP, there is no correlating working embodiment for humans with MBP or PLP for the disease of multiple sclerosis. Applicants have not provided written description of any fragments of MBP or PLP that act as pure bystander antigens in a heterogenous population of humans. There is no direction or guidance for peptides that would provide for antigen-driven bystander suppression. Further, Applicants point to Example 3 as evidence that portions of autoantigens were used as bystander antigens and were successful in conferring tolerance on the treated mice. This is an inaccurate representation of the teachings of Example 3. Example 3 addresses the ability to suppress an OVA response in a co-culture transwell system comprising a co-culture of spleen cells from different animals one set of spleen cells that were derived from animals immunized with MBP/CFA and fed MBP (oral immunization by MBP) and the second, spleen cells from and OVA-fed animals. Example 3, provides MBP derived peptide(s) that suppress OVA spleen cell proliferation. This study is not a *in vivo* study as alleged by Applicants. Example 3 does not demonstrate that any MBP peptide working as an alleged bystander antigen was able to suppress an autoimmune response associated with the autoimmune disease when administered

by an oral or nasal route. The anti-OVA response that was measured was not a response associated with an autoimmune response as claimed. The tolerizing response was not generated using MBP-fed peptides. Therefore, Example 3 of Applicants specification does not, as applicants allege, teach parts of autoantigens that "...not an antigen to which T cells that mediate said disease are sensitized.". Applicants also allege the generality of the bystander response by exemplification of OVA-fed mice to produce non-specific immunosuppressive cytokines. It is noted that the Applicants acknowledge that the response that must be generated by the fed antigen is "oral tolerization" and that it is the oral tolerization to the bystander antigen that generates that non-specific immunosuppressive cytokines. The response to the bystander antigen must be specific and must be tolerizing. Bystander suppression in fact relies upon an antigen specific response. As such, everything the examiner has presented with respect to the unpredictability of "oral tolerization" to any antigen is highly relevant in this case. The general applicability of the art of tolerization is highly relevant here because if one skilled in the art could not predictably tolerize to fed or inhaled antigens, one can not predictably suppress cells to a different antigen (i.e. the bystander effect) by means of elicitation of a OVA-specific tolerization response. Note that Example 3, distinguishes between peptides with non-specific responses and bystander antigen-specific responses. The ability to predictably induce oral tolerization with the bystander antigen to produce regulatory T cells that produce non-specific immunosuppressive cytokines is relevant to the instant case. Unpredictability with

respect to tolerization using any antigen is relevant in this case and is well supported by references provided by the examiner. Suppression is not antigen independent, the tolerizing response of the bystander antigen must be highly specific to the bystander antigen, the biological actions of the cytokines specifically induced by the tolerizing antigen are that which is non-specific to the antigen. While the benefits of the tolerizing response to the bystander antigen may extend to other antigens, it is the induction of the initial tolerization response that must be specifically generated. The generation of a specific tolerizing response to the fed antigen is critical to the generation of the non-specific immunosuppressive cytokines. While the suppression of the heterologous immune response may be non-specific, the generation of the mediators is highly bystander antigen tolerization dependent. Tisch et al (Proc. Natl. Acad. Sci. USA 91: 437-438, 1994) specifically talks about antigen-driven bystander suppression and teach that the induction of antigen-specific CD8+ regulatory T cells is "... an effect that is often variable and highly dose dependent" (page 438, column 1, last paragraph). Tisch et al describes that "While oral administration of antigen appears to be non-toxic, its effects are variable and highly dose specific " and that "It is naive to expect that one form of antigen-specific immunotherapy will be effective in the treatment of all T-cell mediated autoimmune diseases." The applicability of the OVA antigen for a single rodent autoimmune disease remains to be demonstrated to be applicable for the broad treatment of human and rodent autoimmune diseases. The written description of a single bystander antigen that is not tissue

specific and a single autoimmune disease does not provide for evidence that OVA will generate a regulatory T cell response (tolerizing) and similarly effect any other autoimmune diseases. Moreover, it does not provide for written description of a broad category of tolerizing bystander antigens that have similar effects. Thus, in contrary to the declarant's position, the general applicability of OVA to other autoimmune diseases has not been demonstrated by this specification or the declaration. In contrast, to the declarant's opinion, Tisch et al indicate that such a broad sweeping statement is not expected by the art at the time that this application was filed and thus rebuts the opinion of broad applicability by declarant. Applicants have not demonstrated the broad applicability of OVA regulatory T cells to home and suppress any autoimmune disease response as is encompassed by these claims. In any case a fed or inhaled antigen specific T regulatory response must be generated in order to provide for any suppression of heterologous immune responses. Bystander suppression is not antigen independent, bystander suppression specifically depends on an appropriately generated tolerizing response (regulatory T cells) to an heterologous antigen or other antigen to which T cells that do not mediate the disease are generated. Applicants insistence that the suppression is not antigen specific is not correct. The tolerizing T cell regulatory response is specific for the fed antigen, the mediators generated by the tolerizing antigen are generically immunosuppressive. The mediators elicited by the antigen-specific response act generically giving the bystander effect. An antigen specific tolerizing response is required bystander

suppression is not antigen independent, it clearly depends of the ability of the fed antigen to generate a tolerizing response. Applicants have not provided sufficient teachings to generalize OVA tolerance to bystander suppression for any of the other thirty autoimmune diseases. Applicants provide a single bystander antigen for a single autoimmune disease and has not been shown to be broadly generalized as declarant alleges. Turning to the declaration, the declarant attests to the suppression of an immune response using a variety of bystander antigens and alleges that the teachings would be broadly seen by the art. This opinion is refuted by the position of Tisch et al set forth *supra*. It is noted that MBP, PLP and insulin chain data referenced by declarant are all antigens to which T cells that mediate the disease are sensitized in the human and are therefore specifically excluded by the claims. Therefore, what bystander antigens that have written description would be predictably suppress autoimmune disease in humans ? The specification fails to describe any for PLP or MBP fragment that when fed or inhaled acts to generate regulatory T cells that provide for bystander suppression in any rodent model predictive of human therapy. Example 3, fails to provide for written description for any fed or inhaled peptides of MBP that act accordingly. One can not have enabled that which one has not described. Thus, in contrast to what declarant proposes opines, the working embodiments of the specification are limited to tissue specific bystander antigens MBP or PLP in a rodent model of multiple sclerosis (EAE) induced with the opposite antigen, OVA for generic for multiple sclerosis (rodent and human) and a tissue specific bystander antigen,

glucagon for Type I diabetes (rodent and human). Thus, a total of two antigens for two diseases disclosed by means of correlative animal models (OVA, glucagon) for humans and three antigens for rodent EAE disease. The claims encompass a plethora of unknown and undocumented antigens. The claims also encompass at least 30 separate autoimmune diseases. The limited teachings discussed supra, do not provide an adequate written description of the broad genus of either bystander antigens or the broad applicability of a single bystander antigen broadly to a variety autoimmune diseases. OVA-has not been demonstrated to be effective to treat by means of suppression for a variety of autoimmune diseases. Insulin/glucagon/GAD/MBP or PLP have not been demonstrated to be effective as claimed for a variety of autoimmune disorders. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The limited number of bystander antigens useful for specific autoimmune diseases, the lack of demonstration that the disclosed bystander antigens are broadly applicable and sufficient to suppress an autoimmune response in a variety of autoimmune disease fails to enable the broad scope claimed herein for the reasons set forth above.

The rejection is maintained.

5. The provisional rejection of claims 37, 38, 42-44, 46, 48, 49, 52-54, 56 and 57 as previously applied to claims 37-45, 47-55, and 57 as being obvious over 08/461,591 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the

intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

6. The provisional rejection of claims 37, 38, 42-44, 46, 48, 49, 52-54, 56 and 57 as previously applied to claims 37-58 as being obvious over 08/461,662 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

7. The provisional rejection of claims 37, 38, 42-44, 46, 48, 49, 52-54, 56 and 57 as previously applied to claims 37-46 and 48-58 as being obvious over 08/468,996 is maintained for reasons made of record in Paper No. 6, mailed 12-31-96, until a proper terminal disclaimer is filed. The examiner acknowledges the intention of applicants to file a proper terminal disclaimer when allowable subject matter has been identified.

Status of Claims

8. All claims stand rejected.

Allowable Subject Matter

Claim A. A method for suppressing an autoimmune response associated with Type I diabetes in a human or rodent host having said Type I diabetes, the method

comprising administering by mouth to said host an amount of a composition comprising glucagon in an amount effective for suppressing said response.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November

15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
September 29, 2001

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600